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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 10/705,245 | 11/10/2003 | Yuan-Tsong Chen | 16743-003001 / 12A-920716 | 3196 |

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| EXAMINER | |
|---|---|
| KAPUSHOC, STEPHEN THOMAS | |
| **ART UNIT** | **PAPER NUMBER** |
| 1634 | |
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**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/705,245 | CHEN ET AL. | |
| | Examiner | Art Unit | |
| | Stephen Kapushoc | 1634 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *18 June 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1,7-20 and 22-25* is/are pending in the application.

4a) Of the above claim(s) *7 and 13-19* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,8-12,20 and 22-25* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

## DETAILED ACTION

Claims 1, 7-20, 22-25are pending.

Claims 2-6, and 21 are cancelled.

Claims 7, and 13-19 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention. Claim 7 is drawn to a non-elected drug and non-elected allele; Claims 13-19 are drawn to a non-elected invention.

Claims 1, 8-12, 20 and 22-25 are examined on the merits.

Please note: The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

### *Continued Examination Under 37 CFR 1.114*

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 6/18/2007 has been entered.

This Office Action is in reply to Applicants' correspondence of 6/18/2007. Claims 2-6, and 21 is/are cancelled; claims 7, and 13-19 is/are withdrawn as detailed above; no claims have been newly added; claims 1 and 20 have been amended.

Applicants' remarks and amendments have been fully and carefully considered but are not found to be sufficient to put this application in condition for allowance. Any new grounds of rejection presented in this Office Action are necessitated by Applicants' amendments. Any rejections or objections not reiterated herein have been withdrawn in light of the amendments to the claims or as discussed in this Office Action.

This Action is **NON-FINAL**.

***Claim Objections***

2. The objection to claims 1 and 20 as set forth in the previous Office Action for recitation of non-elected subject matter is **WITHDRAWN** in light of the amendments to those claims to remove the recitation of non-elected alleles and drugs.

Applicants have argued (p.7 of Remarks) that claim 12 recites various species of equivalent genetic markers of HLA-B*1502, where applicants have elected the species HLA-Cw*-0801, and that the non-elected species may be examined if the elected species is found allowable. MPEP 803.02. As such the objection to claim 12 as set forth in the previous Office Action is **WITHDRAWN.** It is noted that claim 12 in so far as it requires the elected HLA-Cw*-0801 remains rejected in this Office Action.

***New Claim Rejections - 35 USC § 112 1st ¶ - New Matter***

3. Claims 1, 8-12, 20 and 22-25 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is new matter rejection.

Independent claims 1 and 20 require the limitation that 'the patient is a Mongoloid or a Mongoloid descendent'. However, neither the specification nor claims as originally filed specify that the claimed methods are applied to a Mongoloid or a Mongoloid descendent. Applicants argue (p.6 of Remarks) that support for the limitations of the

rejected claims can be found in the examples of the specification where the specification discloses that the genetic background of the patients studied in the examples is associated with adverse drug reactions. Applicants argue that the skilled artisan would readily pay attention to the races of the individuals studied, that skilled artisan would recognize there are four major racial groups among humans (Sankar et al, 2003), and that the skilled artisan would know that the each of the patients recruited in Taiwan is 'a Mongoloid or a Mongoloid descendent'. These arguments are not found to be persuasive. Initially it is noted that the instant specification recites only that 'patients were recruited either from Chang Gung Memorial Hospital or from other medical centers throughout Taiwan'. There is not indication in the specification that this patient population was made up of individuals of any particular race, nor is there any teaching that, for example, the patient population was in any particular way representative of the Taiwanese population in general. The specification thus provides no indication to the skilled artisan of the demographics of the patient population with regard to race. Furthermore, there is no teaching in the specification that the Applicants specifically contemplate the application of the claimed methods to any one particular race of patients, and no contemplation that the methods are applicable specifically to a patient that 'is a Mongoloid or a Mongoloid descendent'.

For the reasons set forth above, basis for the required limitation that 'the patient is a Mongoloid or a Mongoloid descendent' is not found in the originally filed claims or specification.

The rejection as set forth is **MAINTIANED.**

***Claim Rejections - 35 USC § 112 1st Scope of Enablement***
***Contains new ground of rejection***

4. Claims 1, 8-12, and 22 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for:

> A method for assessing the risk of a Mongoloid patient or Mongoloid descendent patient for developing Stevens-Johnson Syndrome (SJS) or toxic epidermal necrolysis (TEN) in response to carbamazepine (CBZ) comprising determining the presence of an HLA-B*1502 allele in said patient, wherein presence of the allele is indicative of an increased risk for SJS or TEN.

does not reasonably provide enablement for associating any other risk (i.e. a decreased risk) of SJS or TEN with the presence of HLA-B*1502, or the use of any equivalent genetic marker, or profiling comprising determining the presence of thiopurine methyltransferase or long-QT syndrome. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

**Nature of the invention and breadth of the claims**

The claims are drawn to methods for assessing in a Mongoloid or Mongoloid descendent patient any risk of SJS or TEN in response to a carbamazeine by determining the presence of the HLA-B*1502, wherein the presence of the allele is indicative of any risk for the specified adverse reaction.

Claim 11 encompasses the use of any 'equivalent genetic marker', and claim 12, specifies the equivalent genetic marker Cw*0801 (consonant with the election of species).

Claim 22 requires pharmacogenomic profiling comprising determining the presence of thiopurine methyltransferase or long-QT syndrome.

The nature of the invention requires knowledge of a relationship between HLA-B*1502 or an equivalent genetic marker and any risk (i.e. increased risk or decreased risk) of an individual to develop SJS or TEN in response to a carbamazepine. The claims further require knowledge of an association between thiopurine methyltransferase or long-QT syndrome and predisposition of an individual to develop SJS or TEN in response to a carbamazepine.

**Direction provided by the specification and working example**

The specification of the instant application teaches an analysis of HLA-B allele genotype and the development of adverse drug reaction.

The specification teaches that there are various types of adverse drug reactions, and broadly defines 'adverse drug reaction' as an undesired or unintended effect of a drug (p.8, ln.1). The specification teaches that drug eruptions may be mild to moderate in nature (macuolpapular rash, erythema mulitforme, urticaria, fixed drug eruption) or more severe (SJS, TEN) (p.4 lns.10-17).

The specification teaches that there is evidence that adverse drug reactions involve MHC-restricted presentation of drug or drug metabolites.

The specification provides an example of a case:control analysis of HLA-B genotypes and adverse drug reactions in patients recruited from medical centers throughout Taiwan. The specification teaches that the 'cases' were 238 individuals with ADRs, wherein 112 patients were diagnosed with SJS/TEN adverse drug reactions (defining this adverse drug reactions as: SJS is skin detachment of less than 10% of body-surface area; overlap SJS-TEN as 10-30%; TEN as greater than 30%; where SJS, overlap SJS-TEN, and TEN are collectively referred to as SJS/TEN (p. 28, lns 6-15), and 126 individuals had milder reactions to various drugs (p.30 – Example 1). Of the 112 SJS/TEN cases, 42 had carbamazepine-induced SJS/TEN (p.28 ln.6). Controls for the analysis provided in the example were 73 carbamazepine-tolerant patients, and 94 non-patients form the general population (p.28 lns.16-21).

The specification teaches the genotyping of subjects' HLA alleles using PCR amplification with sequence specific oligonucleotides and hybridization of the amplification product to a lineblot (p.28 lns.24-30).

The specification provides an analysis of HLA alleles present in patients with carbamazepine –induced SJS/TEN as compared to patients with milder reactions, the general population, and carbamazepine-tolerant patients (Table 1; p.30 ln.29 – p.31 ln.16). The specification teaches that HLA*B-1502 was detected in 42 of 42 SJS/TEN patients who received carbamazepine, but found only in 3 of 73 carbamazepine tolerant patients, 9 of 142 patients with mild adverse reactions, and 5 of 94 general population subjects. The results indicate that the HLA*B-1502 allele is related to carbamazepine – induced SJS/TEN in a statistically significant fashion (Table 1).

The specification does not teach that the HLA-B*1502 allele is associated, in a statistically significant fashion, with a decreased risk of SJS/TEN in response to carbamazepine.

The specification teaches that 38 of the 42 carbamazepine-induced SJS/TEN patients also had the HLA-Cw*0801 allele. The specification does not provide any statistical analysis of the association of HLA-Cw*0801 with carbamazepine-induced SJS/TEN, nor any analysis of linkage between HLA-B*1502 and HLA-Cw*0801.

The specification does not proved any teachings as to how one would interpret a pharmacogenomic profile comprising thiopurine methyltransferase or long-QT syndrome in the analysis of the predisposition of an individual to develop SJS or TEN in response to a carbamazepine.

**State of the art, level of skill in the art, and level of unpredictability**

Because the claims generically encompass 'equivalent genetic markers' as well as the specific 'equivalent' genetic marker Cw*0801 and thiopurine methyltransferase or long-QT syndrome for which no statistical analysis regarding any association with SJS or TEN in response to carbamazepine has been provided, it is relevant to point out that the prior art of Thisted (1998) provides guidance as to what is required to indicate that an association is statistically significant. Thisted teaches that it has become scientific convention to say that a p-value of 0.05 is considered significant (p.5 - What does it mean to be 'statistically significant'), and that values above the conventional reference point of 0.05 would not be considered strong enough for the basis of a conclusion.

It is unpredictable as to whether or not the presence of any 'equivalent genetic marker' (as generically encompassed by the claims) is useful for determining the presence of the HLA-B*1502 allele or for the assessment of risk of drug adverse reaction. While the specification teaches that 38 of 42 (90%) carbamazepine-induced SJS/TEN patients had an HLA-Cw*0801 allele, there is no statistical analysis of the significance of the association of HLA-Cw*0801 with carbamazepine-induced SJS/TEN, nor any analysis of the linkage of HLA-B*1502 with HLA-Cw*0801. Given that (as expressed in Table 5) the HLA-Cw*0801 allele was found in 13.7% of carbamazepine tolerant individuals and 10.6% of the general population, without any specific analysis of the significance of the association it is not predictable if the presence of the HLA-Cw*0801 allele is a reliable indicator of carbamazepine-induced SJS or TEN. Regarding the linkage of HLA-B*1502 with HLA-Cw*0801, Deng et al (2001) teaches that the traditional criteria are that a Logarithm-of -Odds (LOD) score of > 3.0 is taken as evidence for a significant linkage, a LOD score < -2.0 is taken as evidence against linkage, and a LOD score between -2.0 and 3.0 is not conclusive concerning linkage and exclusion for the genomic region under test (p.314, first full paragraph).

Similarly, the requirement that a pharmacogenomic profiling method includes the analysis of thiopurine methyltransferase or long-QT syndrome is not supported in the specification by example or reference to any well established prior art that either of these genetic factors is reliably associated with a predisposition to SJS or TEN in response to carbamazepine. Without any such established association, it is unpredictable as to how one would interpret a pharmacogenomic profile of a patient with

regard to predisposition to SJS or TEN when the profile includes thiopurine methyltransferase or long-QT syndrome.

**Quantity of experimentation required**

A large and prohibitive amount of experimentation would have to be performed in order to use the inventions in the full scope of the claims. One would have to perform case:control studies to establish that HLA-B*1502 is in some way associated with a decreased risk (as is encompassed by independent claim 1) of SJS or TEN in response to carbamazepine. One would also have to establish that any 'equivalent genetic marker' can be used to predict SJS or TEN in response to carbamazepine, and also establish that HLA-Cw*0801 can reliably predict SJS or TEN in response to carbamazepine. Similarly, one would have to determine how any thiopurine methyltransferase or long-QT syndrome profile could be used in regard to predisposition for SJS or TEN in a pharmacogenomic profile.

**Conclusion**

Taking into consideration the factors outlined above, including the nature of the invention and breadth of the claims, the state of the art, the level of skill in the art and its high level of unpredictability, the lack of guidance by the applicant and the paucity of working examples, it is the conclusion that an undue amount of experimentation would be required to make and use the invention in the full scope in which it is claimed.

**Response to Remarks**

5. Applicants have traversed the rejection of claims under 35 USC 112 1st ¶ for lack of enablement. Applicants have argued (p.8-9 of Remarks) that the claims are limited to

the adverse reactions SJS and TEN, the drug carbamazepine, and the sub-population of Mongoloid or Mongoloid descendent. It is noted that the portion of the rejection drawn to different adverse reactions, different drugs, and different populations are not reiterated in this Office Action and have been withdrawn.

Applicants further argue that the specification defines 'equivalent genetic marker' as a marker 'linked to the allele of interest. However, such a definition does not serve to limit the generic nature of claim, and does not require any particular degree of linkage. As such, the Examiner maintains that the claims encompass the use of a wide variety of diverse genetic markers for which the specification provides no evidence of a reliable or significant association with the required phenotype. Similarly, with regard to the specifically recited HLA-Cw*0801, Applicants argue that the teaching of the specification that 38 of 42 (i.e. 90%) of SJS patients have the recited allele is clearly significant. However the Examiner maintains that without an analysis that takes into account the percentage of carbamazepine-tolerant patients with the recited allele, as well as the percentage of patients in the general population with the recited allele, the specification does not establish a significant and reliable association between HLA-Cw*0801 and a risk of SJS or TEN in response to carbamazepine.

The rejection as set forth is MAINTAINED.

## *Conclusion*

6. No claim is allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Stephen Kapushoc whose telephone number is 571-272-3312. The examiner can normally be reached on Monday through Friday, from 8am until 5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached at 571-272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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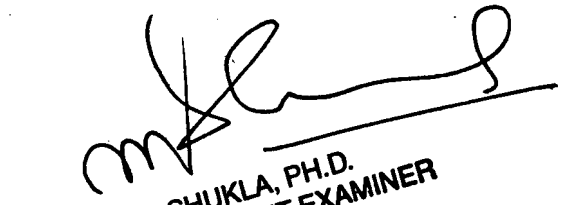
Stephen Kapushoc
Art Unit 1634



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